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10/527,455	10/24/2005	Kozo Takeda	TAKEDA19	2196

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EXAMINER	
SWOPE, SHERIDAN	
ART UNIT	PAPER NUMBER
1652	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/527,455	TAKEDA ET AL.	
	Examiner	Art Unit	
	SHERIDAN SWOPE	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 September 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,5,9-17 and 19-23* is/are pending in the application.

4a) Of the above claim(s) *8, 11-16, 21, and 22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,5,9,10,17,19,20 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' filing of September 9, 2009, in response to the action mailed March 9, 2009, is acknowledged. It is acknowledged that Claim 18 has been cancelled, Claims 1, 4, 9, 10, 19, and 20 have been amended, and Claim 23 has been added. Claims 1, 4, 5, 8-17, and 19-23 are pending. Claims 8, 11-16, 21, and 22 were previously withdrawn from further consideration pursuant to 37 CFR 1.142(b). Claims 1, 4, 5, 9, 10, 17, 19, 20, and 23 are hereby considered.

The elected invention is directed to a method for removing DNA contaminants from a sample comprising an active protein, wherein the method comprises forming DNA particles in a low conductivity and low pH solution (Applicants' response of August 29, 2007).

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Double Patenting

Rejection of Claims 1, 4, 5, 9, 10, 17, 19, and 20 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1, 3, 5, 6, 8, and 13 of US Patent 7,332,289, as described in the prior action, is maintained. Claim 23 is herein rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1, 3, 5, 6, 8, and 13 of US Patent 7,332,289 for the same reasons.

Provisional rejection of Claims 1, 4, 5, 9, 10, 17, 19, and 20 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1, 4, 5, 7, 8, and 14 of US Application 12/018,688, as described in the prior action, is maintained. Claim 23 is herein provisionally rejected under the judicially created doctrine of obviousness-type double

patenting as being unpatentable over Claims 1, 4, 5, 7, 8, and 14 of US Application 12/018,688 for the same reasons.

In regards to the above rejections, it is acknowledged that Applicants' filed a Terminal Disclaimer on September 9, 2009. However, said Terminal Disclaimer has been disapproved because it lists US12/019,688 instead of US12/018,688.

Claim Rejections - 35 USC § 112-Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 4, 5, 9, 10, 17, 19, 20, and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the following reasons.

It is noted that the claims have been amended to remove the phrase "physiologically active protein-containing sample". However, the specification discloses use of the recited method in reference to active proteins. Therefore, the instant claims encompass removal of DNA from a sample of an active protein.

For Claims 1, 19, and 23, the phrase "pH of from 4.0 to the isoelectric point of the protein" renders the claims indefinite. Since proteins can have an isoelectric point below or above pH 4.0, this recitation appears to provide no limitation to the claims. Applicants' response, pg 11, states that this phrase means that "the lower limit of pH is 4.0 and the upper limit of the pH is the isoelectric point of the protein". However, Claims 1, 19, and 23 do not recite what Applicants' assert the phrase means. Claims 4, 5, 9, 10, 17, and 20, as dependent from Claim 1, 19, and/or 23, are indefinite for the same reasons. For purposes of examination, it is assumed that "pH of from

4.0 to the isoelectric point of the protein" means "the lower limit of [the] pH is 4.0 and the upper limit of the pH is the isoelectric point of the protein". Thus, the recited method only encompasses proteins having an isoelectric point above pH 4.

For Claims 4, 5, and 9, it is unclear whether "the aqueous solution" refers to the solution before or after adjusting the ionic strength, as recited in the parent claim.

Applicants' have asserted that the phrase "pH of from 4.0 to the isoelectric point of the protein" means "the lower limit of pH is 4.0 and the upper limit of the pH is the isoelectric point of the protein" (instant response, pg 11). Based on said assertion, Claim 23 is rendered indefinite by recitation of "pH 2.0 to 3.9", as said pH range is not encompassed by Claim 1, from which Claim 23 depends.

For Claim 23, the phrase "adjusting the resulting solution" renders the claim indefinite. It is unclear which solution is being referred to. The skilled artisan would not know the metes and bounds of the recited invention. Claim 20, as dependent from Claim 23, is indefinite for the same reason.

For Claim 23, the phrase "of genetically recombinant protein-containing sample" should be corrected to "of the genetically recombinant protein-containing sample".

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

Rejection of Claims 1, 4, 5, 9, 10, 17, 19, and 20 under 35 U.S.C. 112, first paragraph/written description, for reasons explained in the prior action, is maintained. Claim 23 is

rejected under 35 U.S.C. 112, first paragraph, for the same reasons. In support of their request that said rejection be withdrawn, Applicants provide the following arguments.

(A) The Examiner alleges that the specification teaches no methods for removing DNA contaminants from a sample by forming particles of DNA, wherein the protein remains active after the removal of DNA contaminants.

(B) The specification specifically states at page 13, lines 3-21, that the method involves removing impurities from a physiologically active protein by forming a solution containing the physiologically active protein at a pH equal to or lower than the isoelectric point of the protein, and removing particles formed in the solution.

(C) Specific examples of purifications are shown in Example 2, purification of humanized anti-PTHrP antibody (removal of residual DNA in the eluate) and Example 3, purification of humanized anti-HM1.24 antigen monoclonal antibody (removal of residual DNA).

These arguments are not found to be persuasive for the following reasons.

(A) Reply: The Examiner did not state that "the specification teaches no methods for removing DNA contaminants from a sample by forming particles of DNA, wherein the protein remains active after the removal of DNA contaminants". As stated in the prior action:

> "Said genus encompasses methods for removing DNA contaminants from compositions including cell culture lysates, culture medium, and tissue homogenates. The specification teaches no such methods."

and

> "In addition, the genus encompasses methods for removing DNA contaminants from a sample comprising any active protein, wherein the protein remains active after said removal. The specification teaches only one species of said methods."

Thus, the rejection is based on the specification not describing removal of DNA contaminants from cell culture lysates, culture medium, tissue homogenates and other protein-

comprising samples such that the skilled artisan would recognize possession;. The specification only describes removal of DNA from a sample comprising an affinity purified protein. The rejection is also based on Applicants describing removal of DNA contaminants from only a single type of active protein, i.e, an antibody.

(B) Reply: It is acknowledged that page 13, lines 3-21, assersts that a preferred embodiment involves removing impurities from a physiologically active protein by forming a solution containing the physiologically active protein at a pH equal to or lower than the isoelectric point of the protein, and removing particles formed in the solution. However, said assertion does not describe removing impurities from a physiologically active protein such that the skilled artisan would recognize possession of said method.

(C) Reply: It is acknowledged that Example 2 describes removal of DNA contaminants from the protein-A purified humanized anti-PTHrP Antibody and Example 3 describes removal of DNA contaminants from the protein-A purified humanized anti-HM1.24 antigen monoclonal antibody. However, said two examples are not sufficiently representative of the genus of methods for removing DNA contaminants from any sample comprising any recombinant protein, wherein said any recombinant protein remains active. As explained above and in the prior action, said samples include cell culture lysates, culture medium, and tissue homogenates, while said proteins encompass non-antibody proteins, including enzymes. The specification does not describe said genus of methods such that the skilled artisan would recognize possession.

For these reasons and those explained in the prior action, Claims 1, 4, 5, 9, 10, 17, 19, 20, and 23 are rejected under 35 U.S.C. 112, first paragraph/written description.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Rejection of Claim 10 under 35 U.S.C. 103(a) as being unpatentable over Oxenburch et al, 1965 in view of Kipriyanov et al, 1999, for reasons explained in the prior action, is maintained. Amended Claims 1, 4, and 5 are herein rejected under 35 U.S.C. 103(a) as being unpatentable over Oxenburch et al, 1965 in view of Kipriyanov et al, 1999, for the same reasons.

In support of their request that the prior rejection of (i) Claims 1, 4, and 5 under 35 U.S.C. 102(b) as being anticipated by Oxenburch et al, 1965 and (ii) Claim 10 under 35 U.S.C. 103(a) as being unpatentable over Oxenburch et al, 1965 in view of Kipriyanov et al, 1999 be withdrawn, Applicants provide the following arguments.

(A) The claims have been amended to recite that the method depends on adjusting the pH from 4.0 [up] to the isoelectric point of the protein to be purified. There is nothing in Oxenburgh that even mentions the isoelectric point of the protein.

(B) Additionally, Oxenburgh uses streptomycin to precipitate nucleic acids, which is not needed in the herein claimed method.

(C) The presently claimed method is based upon a new finding that DNA contaminants can be separated as particles from an aqueous solution of a protein-containing sample when the pH of the solution is adjusted to from 4.0 to the isoelectric point of the protein under low conductivity conditions, namely, an ionic concentration of 100 mM or less. This particle formation,

remarkably, can be visually observed. Therefore, satisfying each limitation the claimed method is critical to the claimed method in order to remove DNA contaminants effectively from a sample without the need for a complicated process such as a chromatographic treatment.

(D) The protein is now recited as a "genetically recombinant protein", which was not even contemplated by Oxenburgh in 1965. There is nothing in either Oxenburgh or Kipriyanov, taken alone or together, that even suggests that DNA contaminants dissolved in solution can be insolubilized and removed under conditions of specific pH and ionic concentration ranges.

These arguments are not found to be persuasive for the following reasons.

(A) Reply: It is acknowledged that the claims have been amended to recite adjusting the pH of the solution, wherein, according to Applicants' instant response, "the lower limit of [the] pH is 4.0 and the upper limit of the pH is the isoelectric point of the protein". Oxenburch et al teaches setting the pH to within the range 6-8. Thus, Oxenburch et al encompasses methods wherein the solution is set to a pH between 4 and any protein having an isolectric point of between 6 and 8. Many proteins, including many of the recombinant antibodies of Kipriyanov et al would have an isolectric point between 6 and 8. Thus, the steps of Oxenburch et al render Applicants' method obvious in view of Kipriyanov et al.

(B) Reply: Claim 1 recites a method "which comprises the steps of:…", which does not exclude the use of streptomycin.

(C) Reply: The method of Oxenburch et al encompasses setting the protein-containing solution to the low ionic strength (Fig 1) and setting the pH to between 6 and 8 (pg 1417; parg 3). Said pH range is between 4 and the isoelectric point of many proteins.

The instant claims do not recite the formation of particles that can be visually observed.

The instant rejection is not based on chromatographic treatment. Nonetheless, the claims do not exclude using a sample comprising a chromatographically isolated protein. In fact, the specification fails to teach removal of DNA contaminants from any protein-containing solution where the protein has not been first chromatographically purified.

(D) Reply: It is acknowledged that the skilled artisan would not have contemplated a recombinant protein in 1965. Therefore, rejection of Claims 1, 4, and 5 is now under 35 U.S.C. 103(a). As explained in the prior action, Oxenburch et al teaches that DNA can be precipitated from a protein-containing solution by setting the solution to low ionic strength and a pH of 6-8 (Fig 1; pg 1416, parg 11, to pg 1417, parg 3).

Rejection of Claim 17 under 35 U.S.C. 103(a) as being unpatentable over Oxenburch et al, 1965 in view of Somack et al, 1999, for reasons explained in the prior action, is maintained. In support of their request that said rejection be withdrawn, Applicants provide the following arguments.

(A) Even though Somack discloses that precipitated DNA can be removed by filtration, Oxenburgh does not disclose how to form this DNA precipitate.

(B) There is nothing in Oxenburgh that even suggests adjusting the pH and the isoelectric point of a solution in order to precipitate DNA.

(C) Oxenburgh did not even contemplate solutions of recombinant proteins.

These arguments are not found to be persuasive for the following reasons.

(A) Reply: The skilled artisan would have known that precipitated DNA can be removed by filtration, regardless of the method used for the precipitation. As explained in the prior action, Oxenburch et al teaches a method for removing DNA contaminants from a protein-

containing bacterial lysate, wherein the method comprises forming DNA particles, in a low ionic strength, pH 6-8 solution, followed by removing the precipitated DNA particles.

(B) Reply: Oxenburch et al teaches adjusting the pH of the solution (pg 1417, parg 3). Solutions do not have isoelectric points.

(C) Reply: It is acknowledged that the skilled artisan would not have contemplated a recombinant protein in 1965. Therefore, rejection of Claims 1, 4, and 5 is now under 35 U.S.C. 103(a).

Rejection of Claim 18 under 35 U.S.C. 103(a) as being unpatentable over Oxenburch et al, 1965 in view of what was well-known in the art, is rendered moot, as said claim has been cancelled.

Rejection of Claims 9 and 19 under 35 U.S.C. 103(a) as being unpatentable over the combination of Oxenburch et al, 1965 and Kipriyanov et al, 1999 in view of Harlow et al, 1988, as evidenced by Fahrner et al, 1999, for reasons explained in the prior action, is maintained. Amended Claim 20 is herein rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Oxenburch et al, 1965 and Kipriyanov et al, 1999 in view of Harlow et al, 1988, as evidenced by Fahrner et al, 1999, for the same reasons and because Harlow et al teaches the use of Tris buffer to adjust the pH (pg 310).

In support of their request that said rejection of Claims 9 and 19, as well as the prior rejection of Claim 20, be withdrawn, Applicants provide the following arguments. There is absolutely nothing in any of the cited references that even suggests considering the isoelectric point of the solution when precipitating DNA contaminants. It is critical to the herein claimed method that both the pH and the ionic concentration be adjusted in order to precipitate DNA

contaminants from a solution. This is neither shown nor suggested by any of the cited references, either alone or in combination.

These arguments are not found to be persuasive for the following reasons. Solutions do not have isoelectric points; proteins do. As explained above, Oxenburch et al teaches adjusting the ionic strength and pH of the solution (pg 1416, parg 10-11 and pg 1417, parg 3). Oxenburch et al also teaches that their method is effective in the range of pH 6-8 (pg 1417, parg 3), which is between pH 4 and the isoelectric point of many antibodies.

Rejection of Claims 1, 4, 5, 9, 10, 18, and 19 under 35 U.S.C. 103(a) as being unpatentable over Lydersen et al, 1994 in view of Harlow et al, 1988, as evidenced by Fahrner et al, 1999, as explained in the prior action, is maintained. In support of their request that said rejection be withdrawn, Applicants argue that there is nothing in the combination of Lydersen, Harlow and Fahrner that even suggests that DNA contaminants can be precipitated by controlling both the pH and the ionic concentration. This argument is not found to be persuasive for the following reasons. Using the method of Harlow et al followed by the method of Lydersen et al would have been obvious to the skilled artisan and, as explained in the prior action, motivation to do so derives from the desire to remove the DNA contaminants in protein A-sepharose isolated antibodies (see Fahrner et al; Table I). Removal of said DNA contaminants is advantageous in the preparation of antibodies for treatment. The combined method of Lydersen et al and Harlow et al results in adjusting the solution to low ionic strength (Harlow) and adjusting the solution to pH 4-5.5 (Lydersen et al; Fig 4), which is between pH 4 and the isoelectric point of many proteins.

Rejection of Claim 17 under 35 U.S.C. 103(a) as being unpatentable over the combination of Lydersen et al, 1994, Harlow et al, 1988, and Fahrner et al, 1999 in view of Somack et al, 1999,

for reasons explained in the prior action, is maintained. In support of their request that said rejection be withdrawn, Applicants argue that none of these references suggests that DNA contaminants can be precipitated form a protein-containing solution by controlling pH and isoelectric point along with the ionic concentration. This argument is not found to be persuasive for the reasons explained above regarding rejection of Claims 1, 4, 5, 9, 10, 18, and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lydersen et al, 1994 in view of Harlow et al, 1988, as evidenced by Fahrner et al, 1999

Rejection of Claim 20 under 35 U.S.C. 103(a) as being unpatentable over the combination of Lydersen et al, 1994, Harlow et al, 1988, and Fahrner et al, 1999 in view of Sigma, Inc, as described in the prior action, is maintained. In support of their request that said rejection be withdrawn, Applicants provide the following arguments. (i) The fact that Sigma teaches an aqueous solution of 500 mM Tris at pH 3.5-5.0 adds nothing to the cited references. There is no suggestion for using the Sigma solution in any of the methods of the cited references. (ii) Moreover, there is no teaching or suggestion for controlling the pH/isoelectric point and ionic concentration of the solution to be treated.

These arguments are not found to be persuasive for the following reasons. (i) The skilled artisan would have known that, subsequent to or in conjunction with the method of Harlow et al, the pH adjustment of Lydersen et al could have been accomplished with the 500mM Tris buffer, pH 3.5-5.0, of Sigma, Inc.

For these reasons and those set forth in the prior action, the above rejections under 35 U.S.C. 103(a), are maintained.

Allowable Subject Matter

No claims are allowable.

Applicant's amendment necessitated any new grounds of rejection presented in this Office action. Any new references were cited solely to support rejection(s) based on amendment or rebut Applicants' arguments. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Regarding filing an Appeal, Applicants are referred to the Official Gazette Notice published July 12, 2005 describing the Pre-Appeal Brief Review Program.

Final Comments

To insure that each document is properly filed in the electronic file wrapper, it is requested that each of amendments to the specification, amendments to the claims, Applicants' remarks, requests for extension of time, and any other distinct papers be submitted on separate pages. It is

also requested that the serial number of the application and date of amendment be referenced on every page of the response.

It is also requested that Applicants identify support, within the original application, for any amendments to the claims and specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 571-272-0943. The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published application may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on the access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SHERIDAN SWOPE/
Primary Examiner, Art Unit 1652